Overall Systems Analysis of the Carotid Sinus Baroreceptor Reflex Control of the Circulation

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THE entire circulatory system constitutes a closed hydraulic loop, and blood circulates within this entire system. The system serves to deliver oxygen and nutrients to all cells of the body. Quite apart from delivering life-sustaining nutrients to the cell, the system permits the removal of waste and byproducts of metabolism. In addition, the cardiovascular system serves as a communication network, the purpose of which is to carry molecules from organ system to organ system, and from organ system to the cells. Ultimately, the system is a transport system, and the major determinant of how well the system performs its transport role is blood flow or cardiac output.

To understand how the nervous system, particularly the high-pressure baroreceptors, control the pressures, volumes, and flows in the intact circulation, one must first understand the basic mechanical properties of the individual major subcompartments. With this knowledge, we have a clearer understanding of the role of the baroreceptor in the intact circulatory system.

From a systems point of view, we can consider the entire circulatory system to consist of two major compartments, the heart-lung compartment and the systemic vascular bed compartment. Each compartment interacts mechanically with the other, in a relatively complex manner, to give the various pressures, volumes, and flows in the intact circulation. To quantitatively understand the relationships between arterial and venous pressures, blood volumes, and cardiac output, a model of the circulatory system is shown in figure 1. Although this model can be used to integrate a great deal of physiologic information, it contains many assumptions and simplifications of the real system. Despite this, it can greatly contribute to our understanding of overall circulatory mechanics and the role of the baroreceptors in the control of the circulation. This is not a unique model, nor is it the only model configuration that can explain overall circulatory regulation. I chose it because, conceptually, it contains all the major segments of the circulation, and lends itself easily to a graphic analysis that will be discussed later.

Heart-Lung Compartment

Shown in the upper part of figure 2 is an anatomic representation of the heart-lung compartment. The lower half shows a block, or systems diagram, of the heart-lung compartment. Cardiac output is selected as the output variable of the system. Likewise, right atrial and arterial pressures are selected as the input variables. The choice of right atrial and arterial pressures and cardiac output as the input-output variables is dictated by the constraint that the total blood volume of the entire circulation is a constant. This will be discussed further when we analyze the systemic vascular bed. With this model, the effect of the input variables, right atrial and arterial pressures, on the output variable, cardiac output, can be determined.

Figure 3 demonstrates the effects of right atrial pressure on cardiac output in the isolated heart-lung compartment. This direct effect of right atrial pressure on cardiac output is better known as Starling’s Law of the Heart, and the relationship is called the Starling curve for the heart-lung compartment. Note that arterial pressure, the other input, was assumed to remain constant. The reason for this is that arterial pressure will inversely affect the cardiac output itself. Therefore, if the arterial pressure is fixed, the relation between right atrial pressure and cardiac output will not be confounded with changes in arterial pressure.

Figure 4 shows the Starling curve relationship at various arterial pressures. To obtain this family of curves, the arterial pressure is fixed at the various levels shown, and the right atrial pressure is changed while measuring...
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HEART-LUNG COMPARTMENT

SYSTEMIC VASCULAR COMPARTMENT

Fig. 1. Anatomic representation of the entire circulatory system. The heart-lung compartment contains the left and right hearts and the pulmonary vascular bed, which is considered as a flow generating system. The systemic vascular bed compartment contains arterial and venous capacitances, which are connected by total peripheral resistance. $P_a =$ arterial pressure; $P_{ra}$ = right atrial pressure; $P_v =$ venous pressure.

the cardiac output. Although the actual effects are exaggerated in the figure for illustrative purposes only, it indicates that, for any given right atrial pressure, the cardiac output will decrease when arterial pressure is increased. This is a consequence of the "afterload" effects on the performance of the left ventricle. Right atrial and arterial pressures are not the only determinants of the Starling curve. Although not specifically designated in the system diagram (fig. 2) as inputs, the heart's contractility or inotropic background, sympathetic nervous control, and coronary perfusion also alter the Starling curve. Figure 5 shows the effects of either increasing or decreasing the inotropic background of the heart on the cardiac output-right atrial pressure relationship.

Thus far, we have analyzed the heart-lung compartment as a flow-generating pump in isolation from the systemic circulation. In the above analysis, we have considered the heart-lung compartment to be a single flow-generating compartment that is dependent on right atrial pressure, arterial pressure, and inotropic state. No mechanistic interactions between the heart-lung compartment and systemic vascular bed compartment have yet been considered. Because the entire system is coupled or joined under normal conditions, we must also understand the function of the other system, i.e., the systemic vascular bed. Only then can the two compartments be put together to provide a composite of the entire circulation.

Systemic Circulation Bed Compartment

Shown in figure 6 is an anatomic and systems block diagram of the vascular bed. We have chosen the independent variable to be flow and the dependent variables to be arterial and venous pressures. This choice of input-output variables for the systemic vascular bed compartment is not done arbitrarily. Because our eventual aim is to couple the heart-lung compartment with the systemic vascular bed compartment, we choose the output variable(s) of one system to be the input variable(s) of the other system. This choice will then allow for the direct coupling of the two systems.

To determine the effects of flow, the input variable, on arterial and venous pressures, the output variables, we will perform an experiment in which the heart is replaced with a controllable perfusion pump. We will

Fig. 2. Anatomic representation (top) and systems diagram (bottom) of the isolated heart-lung compartment. The arrow entering the block in the systems diagram represents an input to the system, and the arrow exiting the block represents an output to the system.

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assume that the total blood volume and resistance is constant in the systemic vascular bed.

We will first consider the situation in which the perfusion pump is not pumping at all, and there exists normal arterial and venous smooth muscle tone and a normal amount of total blood volume. Under these conditions, the blood will stress the vascular wall and cause a uniform static pressure throughout the systemic vascular bed, because the vascular system does not have an infinitely large compliance. This static pressure first drew Starling's attention, then that of Starr and Rawson, and finally was measured by Guyton et al. to be about 7 mmHg. This baseline static pressure has been defined by Guyton to be the mean systemic filling pressure. It is the pressure in the vascular bed when flow throughout the vascular bed is zero. When we plot arterial and venous pressures independently on the ordinate axis and flow on the abscissa, the static mean systemic filling pressure will be found on the ordinate (fig. 7). As the perfusion pump begins to pump, blood is transferred from the veins to the arteries. This transfer of blood causes an increase in the arterial pressure that is proportional to the flow, and a concomitant decrease in venous pressure. A very important question is "Why is there a concomitant decrease in venous pressure?" Because the total blood volume is constant, the increase in arterial pressure causes and increase in arterial blood volume and, therefore, venous blood volume must decrease, causing a decrease in venous pressure. As seen in the diagram (fig. 7), the decrease in venous pressure is not equal to the increase in arterial pressure. Despite the fact that equal blood volumes have been transferred, the relative magnitudes of the changes of arterial and venous pressure are inversely related to the compliances of these two vascular segments. In addition, the pressure gradient, the arterial minus the venous pressures, divided by the flow is the total peripheral resistance of the vascular bed.

The development of these two relationships is critical to the understanding of the systemic vascular bed. The relationship not only describes the resistance properties of the systemic vascular bed, it describes the capacitance properties of the arterial and venous segments. The relative slopes of the arterial pressure-flow relation to the venous pressure-flow relations are inversely proportional to the compliances of the arterial and venous segments. Also, the ratio of the slopes of the arterial pressure-flow relationship to the venous pressure-flow relationship is the ratio of the venous to arterial compliance. It should also be noted that the arterial pressure-flow relation determines the afterload on the left ventricle, and the venous pressure-flow relation deter-

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Fig. 5. Effects of changes in contractility on the Starling relationship in the isolated heart-lung compartment.

mines the preload on the right ventricle. This venous pressure-flow relationship has been defined by Guyton as the venous return curve.\textsuperscript{10}

**Total System**

How can we integrate the two compartments, the heart-lung and systemic vascular bed, into a model of the entire circulatory system? In the natural circulation, the heart-lung compartment is coupled with the systemic vascular bed, and the blood flow is equal to the cardiac output. Also, the blood flow returning from the veins, the venous return, under steady state equilibrium conditions is equal to the cardiac output. Therefore, the intersection of the Starling curve for the heart and the venous return curve for the systemic vascular bed defines the equilibrium operating point (fig. 8). However, this analysis will only give us the values of cardiac output and venous pressure, without much insight into what is causing the changes to take place, as well as the interactions and control of the circulation. To understand how cardiac output and venous pressure are reached and how other segments of the circulation effects the equilibrium point, a more detailed model of the systemic circulation is needed.

This can be accomplished in either of two ways. The first is that detailed equations of the characteristics of each compartment can be written and then solved simultaneously. The second is a graphic approach that I wish to discuss in some detail. This approach was first developed by Togawa,\textsuperscript{11} and has been used in con-

junction with a physical hydraulic model at the author's institution to teach postdoctoral fellows, graduate students, medical students, and undergraduate students integrated cardiovascular function over the past 15 yr.

As can be seen in the anatomic model of figures 1 and 6, the systemic vascular bed consists of three segments: arterial and venous capacitances and total peripheral resistance. These anatomic segments can be represented by their corresponding two-dimensional graphs. Figure 9 shows the graphic representations of these three segments. For example, the venous capacitance is represented by the relationship of venous pressure and venous volume. The inverse slope of the relationship represents the venous compliance, and the intercept on the venous volume axis is the unstressed vascular volume. The graphs are drawn linearly for illustrative purposes only; nonlinear relationships will not change the graphic method of analysis. As will be shown later with physiologic experimental evidence, the relationships have been found to be nonlinear, especially during baroreceptor reflex system regulation.

The graphs of the three individual vascular segments can be solved graphically to obtain the relationship between venous pressure and flow. As was discussed previously, this relationship is the venous return curve. To make the graphic solution easier, the individual

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graphs of each of the segments are appropriately rotated, and then combined into appropriate quadrants, as shown in figure 10. Note the axes common to the third and fourth quadrants algebraically sum to a constant value. Also note that the slopes of the arterial pressure-volume relationship and the venous pressure-volume relationship are nearly equal, which implies that they have equal compliances. However, this is not the case. Because the full-scale magnitudes of the respective pressure axes are 0–300 mmHg for arterial pressure and 0–10 mmHg for venous pressure, the ratio of the venous to arterial compliances, as shown in figure 10, is 30:1.

To derive the venous return curve in figure 10, I chose a flow, in particular, flow \( F_1 \), in quadrant 2. At a flow of \( F_1 \), the mean arterial pressure is \( P_{A1} \). In quadrant 3 with a particular arterial pressure \( P_{A1} \), we can expect a particular arterial blood volume, \( V_{A1} \), to exist. As noted previously, the axis common to the 3rd and 4th quadrants has two scales, one on the left side and the other on the right side. The sum of the adjacent values on the two scales is a constant. Therefore, when the blood volume in the arterial segment is increased by an amount \( \delta V \), the blood volume in the venous segment must decrease by the same amount. This doubly scaled axis represents the physiologic situation that the total blood volume in the systemic vascular bed is constant. With a particular \( V_{A1} \), the venous blood volume is \( V_{V1} \). This venous blood volume will yield a venous pressure of \( P_{V1} \). The initial flow \( F_1 \) and venous pressure \( P_{V1} \) represent one point on the venous pressure-flow curve (venous return curve) in quadrant 1. We can choose another flow and similarly determine a venous pressure that will correspond to the particular flow by going around the four quadrants counterclockwise, as shown in figure 10. If enough points are obtained, a line can be drawn through them, yielding the venous return curve.

It should be obvious that, if the total peripheral resistance, the slope of the arterial pressure-flow relation in quadrant 2, were to change, we would then have a different venous return curve. This would also be true for either the arterial or venous capacitances. The venous return curve is dependent on the intercepts, slopes, and shapes of the relations in quadrants 2, 3, and 4, namely, the total peripheral resistance, the arterial and venous capacitances. Any changes that occur to these three relations would then cause changes in the venous return curve. This fact is extremely important, because the baroreceptor reflex system does effect and change all three relations.

It should be recalled that the cardiac output is the output variable of the heart-lung compartment, and it...
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Fig. 9. Graphical representation of the three individual segments that make up the systemic vascular bed compartment.

is also the input variable of the systemic vascular bed. Similarly, the outputs of the systemic vascular bed, arterial, and venous pressures are the inputs to the heart-lung compartment. These variables must be in equilibrium with each other. With this in mind, we can now answer the question, “How can we integrate the two systems and find the equilibrium values?”

This can be accomplished by simply drawing the Starling curve, the functional relationship for the heart-lung compartment, into quadrant 1, as shown in figure 11. We can superimpose the heart-lung function curve into quadrant 1 because the output variable was chosen as cardiac output, and its input variable was chosen as the right atrial pressure. In the intact circulatory system, mean right atrial pressure is equal to mean venous pressure, and the cardiac output of the heart-lung compartment is equal to the flow into the systemic vascular bed. The point at which the Starling curve crosses the venous return curve is the equilibrium point for the two compartments when they are coupled together. The cardiac output, the arterial and venous pressures, and the arterial and venous volumes can be now read directly from their corresponding axis.

It is fairly safe to say that one would be able to predict what changes would occur to cardiac output, arterial and venous pressure, and arterial and venous volumes if, and only if, one change occurs in either the systemic vascular bed or the heart-lung compartment. However, if multiple changes occur in both compartments, it would be nearly impossible to predict the effects on cardiac output, arterial and venous pressure, and arterial and venous volumes. This is exactly what happens to the entire circulatory system when a disturbance occurs; that is, in response to the given disturbance, the reflex system(s) change the various parameters of the heart-lung compartment (inotropic background) and the systemic vascular bed (total peripheral resistance and arterial and venous capacitances) until a new and stable equilibrium is reached.

I hope that I have generated enough curiosity in the readers of this article for you to attempt to change one or more of the parameters and predict the directional changes of the variables. For example, just increasing total peripheral resistance (decreasing the slope of the arterial pressure-flow relation in quadrant 1), it will be found that the equilibrium cardiac output will decrease, the arterial pressure and volume will increase, and venous pressure and volume will decrease.

Carotid Sinus Reflex Control of the Circulation

One of the primary controllers of arterial blood pressure and cardiac output is the carotid sinus arterial baroreceptors. Although many of the studies in the past have concerned themselves with the carotid sinus baroreceptor reflex control of individual parameters, such as heart rate, contractility, and total peripheral resistance, there is a relative paucity of information on the reflex control of the Starling and venous return curves.

Shown in figure 12 is the Starling curve and venous return curve simultaneously obtained in a 22-kg canine. These function curves were obtained while controlling the carotid sinus pressure at three different levels. As can be easily seen, there are nearly parallel upward
shifts in the venous return curve when the carotid sinus pressure is decreased. These upward shifts in the curve cause the equilibrium cardiac output to increase because of the higher sympathetic drive to both the vessels and the heart. Also evident is the absence of any apparent changes in the Starling curve. This is opposite to what was shown previously in the model analysis for the heart-lung compartment alone, and it could be erroneously concluded that the reflex does not affect the Starling curve relationship when the two compartments are coupled. We will discuss the reason for this lack of apparent change in the Starling curve by the baroreceptor reflex system later.

One would assume the parallel shift of the venous return curve by the reflex system is caused solely by a change in the systemic vascular capacitance; in particular, a change in the unstressed vascular volume of the venous segment of the circulation. From the model analysis, a decrease in the unstressed vascular volume, shifting the pressure-volume relationship of the venous segment upward without a change in slope, will cause a parallel upward shift in the venous return curve. However, this is not entirely true, as will be explained next. We know from previous work that the reflex system affects all the segments of the systemic vascular bed. Figure 13 shows the results of an experiment in which blood volume shifts were measured in both the systemic and pulmonary vascular beds. This is accomplished by placing reservoirs between the animal and the extracorporeal circuit at the junctions of the vena cava, as well as the left atrium, and perfusing at constant blood flow. In the experiment shown in figure 13, when intrasinus pressure was lowered from 200 to 50 mmHg, the blood volume in the systemic vascular reservoir increased approximately 275 ml, indicating that there was a decrease in systemic venous vascular capacitance. Blood volume in the pulmonary vascular bed also decreased, as indicated by an increase in pulmonary reservoir volume. Also evident from the figure is the increase in systemic arterial and pulmonary arterial pressures, indicating that there was an increase in both the systemic vascular and pulmonary vascular resistance.

The fact that total systemic vascular resistance changes with the baroreceptor reflex has been clearly shown previously; however, there has been very little information published on the shape of the arterial pressure-flow relationship. Shown in figure 14 is an example of a steady state arterial pressure-flow at carotid sinus pressures of 50, 125, and 200 mmHg. The arterial pressure-flow relationship at any given carotid sinus pressure is found to be nonlinear. The steady state arterial pressure-flow relationship shifted upward and
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Fig. 12. Experimentally determined Starling curve and venous return curve at carotid sinus pressures of 50, 125, and 200 mmHg.

shift is indicative of an increase in resistance calculated either incrementally or as total peripheral resistance. In addition, the zero flow arterial pressure was found to increase when the carotid sinus pressure was decreased.15 Unlike the systemic vascular bed, the pulmonary arterial pressure-flow relationships were linear over a wide range of flows, and the reflex system shifted the pressure-flow relations in a nearly parallel manner.

An important question is "What effect does an increase in systemic vascular resistance have on the venous return curve?" The answer to this question was stated previously, and can be easily obtained from the model analysis of the circulation. If one only increases the total peripheral resistance (for the model, it is done by only decreasing the slope of the pressure-flow curve in quadrant 2) and reconstructs the venous return curve, it will be apparent that the slope of the venous return curve decreases. This is clearly opposite to what happens to the physiologic measured curve shown in figure 12.

Fig. 13. Experimental recording of systemic and pulmonary vascular beds when carotid sinus pressure is changed between 50 and 200 mmHg.

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This difference in model outcome and physiologic response had prompted us to investigate the potential reasons for this discrepancy. It can be shown, from the model analysis, that decreasing the venous segment compliance (defined as the slope of the venous pressure-volume relationship) would cause the slope of the venous return curve to decrease. However, in several published studies using a "black box" approach, the total systemic vascular compliance changed very little with the carotid sinus baroreceptor reflex, whereas we found that the reflex did significantly affect the unstressed vascular volume, a parallel shift of the venous segment pressure-volume relationship. In the above study, blood volume changes were measured in external reservoirs, while the circulation was perturbed in different manners. Regardless of how quantitative this study was, it is an attempt to delineate mechanisms within the circulation by estimating them from measurements taken external to the system. Because of the architectural complexity of the systemic vascular bed and the nonlinearity of the neural control, it is nearly impossible to decide on any single mechanism involved in vascular capacitance control using this black box approach.

There is, however, ample evidence indicating that the venous vessels of the microcirculation could be responsible for the capacitance changes seen in the overall circulation by the baroreceptor reflex system. To test the hypothesis that venules in the microcirculation are responsible for the capacitance changes in the circulation, we measured the pressure-diameter relationship of 20–200-μ venules in the intestine of the rat when the baroreceptor reflex system was activated. As shown in figure 15, the pressure-diameter relation significantly shifts to the left with a small but significant shift in the slope of the curve. These results were qualitatively the same in all vessels studied; however, there were quantitative differences in the magnitude of these changes. These results strongly indicate that the intercept of the pressure-diameter relation, which is similar to the unstressed vascular volume, is under sympathetic control. Furthermore, the slope of the relation, which is similar to the compliance, is also under neural control, but to a lesser extent. As previously stated, from the model analysis, the net effect of decreasing the unstressed vascular volume and the compliance would be to shift the venous return curve upward and decrease its slope. Decreases in unstressed vascular volume are consistent with observed parallel changes in the venous return curve, whereas increases in total peripheral resistance and decreases in compliance are inconsistent with the measured venous return curve. The answer to this inconsistency may be found in quadrant 3, the arterial pressure-volume relationship.

Again, it can be easily shown from the model analysis that decreasing the compliance of the arterial segment

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Fig. 14. Steady state arterial pressure-flow relationship at carotid sinus pressures of 50, 125, and 200 mmHg.

Fig. 15. Pressure-diameter relationship of an intestinal microvascular venule at normal and increased sympathetic tone. □ = pressure-diameter relationship at normal sympathetic tone; □ = prior to increased tone; ○ = after increased tone; ■ = pressure-diameter relationship at increased sympathetic tone.
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Fig. 16. Carotid sinus baroreceptor reflex control of the Starling curve when the arterial pressure is controlled at 100 mmHg.

of the circulation would, theoretically, cause an increase in the slope of the venous return curve. We, therefore, hypothesize that the reflex system: (1) decreases arterial compliance, in conjunction with (2) decreases in the venous compliance, and (3) increases in total peripheral resistance. The net effect of these three actions has a canceling effect on the slope of the venous return curve, and, therefore, we are unable to measure any significant changes in the slope of the venous return curve. Preliminary evidence from our laboratory indicates that the carotid sinus baroreceptor reflex system does change the arterial segment compliance. When sympathetic tone is increased, the arterial segment compliance does decrease. More quantitative data is needed for us to determine if the magnitude of the decreases are large enough to offset the effects of increases in total peripheral resistance and decreases in venous compliance.

Let us now turn our attention to the reflex regulation of the Starling curve. As noted previously in figure 12, there is, seemingly, a lack of reflex control of the heart-lung compartment, because there are no apparent changes in the Starling curve. From years of accumulated knowledge, this is obviously not true. As explained previously, there are two opposing effects on the heart-lung compartment when the reflex is activated. An increased sympathetic drive to the heart will increase the cardiac output, whereas an increase in total peripheral resistance will increase the arterial pressure or afterload that will decrease the cardiac output. Because both these effects are simultaneously present when the reflex is activated, the Starling curve shown in figure 12 shows no significant differences. To test if the reflex does have significant effects on the Starling curve, it would be necessary to maintain the arterial pressure constant. Shown in figure 16 is an example of one such experiment. The Starling curve was obtained at the same three carotid sinus pressures; however, the arterial blood pressure was fixed at 100 mmHg. The results indicate a clear separation of the Starling curve at the three different carotid sinus pressures, which is indicative of sympathetic reflex control of the heart-lung compartment. These findings are similar to those previously reported using entirely different techniques.

The carotid sinus baroreceptor reflex changes the sympathetic drive to the heart-lung compartment to such an extent that cardiac output remains nearly constant, despite the increase in total peripheral resistance and arterial pressure afterload.

I hope that it is clear that the carotid reflex system has control over nearly every segment of the circulation. My institution has, and is currently using, a systems approach to study the reflex control in conjunction with a variety of physiologic and modelling techniques. The differences between the model outputs and physiologic data have led us into further investigations of potential mechanisms by which the reflex system controls the entire circulatory system. It is hoped that this brief review will stimulate even further investigations, because there are many open questions still to be answered.

References


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